General

Guideline Title

Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay). London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 10. 46 p. (Diagnostics guidance; no. 20).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

There is currently insufficient evidence to recommend the routine adoption in the National Health Service (NHS) of the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. The tests show promise and further research to provide robust evidence is encouraged, particularly to demonstrate the value of using the test results in clinical decision-making (see Sections 5.18 to 5.22 of the original guideline document).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Bloodstream infection
- Sepsis

Guideline Category

Diagnosis

Technology Assessment

Clinical Specialty

Critical Care

Infectious Diseases

Pathology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Hospitals

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of using the LightCycler SeptiFast Test MGRADE, SepsiTest, and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi

Target Population

Adults and children (of any age) with suspected blood stream infections in secondary care (i.e., departments and wards providing care for acutely unwell patients and/or critical care units) who required blood cultures

Interventions and Practices Considered

Tests for rapidly identifying bloodstream bacteria and fungi performed on whole blood samples in conjunction with clinical assessment:

- LightCycler SeptiFast Test MGRADE
- SepsiTest
- IRIDICA BAC BSI assay

Note: These tests are currently not recommended (see the "Major Recommendations" section).

Major Outcomes Considered

- Intermediate outcomes
    - Accuracy of diagnostic tests
    - Discordant results with blood culture
    - Time to result
    - Time to treatment
    - Test failure rates

    - Duration of intensive care unit (ICU) and/or hospital stay
    - Duration of broad and narrow spectrum antimicrobial therapy
    - Re-admission rate
    - Change in antimicrobial treatment plan
- Clinical outcomes
    - Side-effects associated with broad spectrum antimicrobial use
    - Morbidity and mortality
    - Severity of disease (as measured by scoring systems such as the Acute Physiology and Chronic Health Evaluation [APACHE] II, Simplified Acute Physiology Score [SAPS] II and the Sequential Organ Failure Assessment [SOFA]]
    - Rates of superinfection
    - Rates of resistant infections
    - Health-related quality of life
- Cost-effectiveness outcomes

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

A systematic review of the literature and meta-analysis (where appropriate) was undertaken to evaluate the clinical effectiveness of the SeptiFast, SepsiTest and IRIDICA assays in conjunction with clinical assessment for rapidly identifying bloodstream bacteria and fungi.

A review and meta-analysis was undertaken in accordance with the guidelines published by the Centre for Reviews and Dissemination (CRD) for undertaking systematic reviews and the Cochrane Diagnostic Test Accuracy Working Group on the meta-analysis of diagnostic tests.

Methods for Reviewing Effectiveness

Identification of Studies

Electronic Databases

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (OvidSP) 1948 to May 2015
- EMBASE (OvidSP) 1980 to May 2015
- Cochrane Database of Systematic Reviews (Wiley Online) 1996 to May 2015
- Cochrane Central Register of Controlled Trials (Wiley Online) 1898 to May 2015
- Health Technology Assessment Database (Wiley Online) 1995 to May 2015
- Database of Abstracts of Review of Effects (Wiley Online) 1995 to May 2015
- National Health Service (NHS) Economic Evaluation Database (Wiley Online) 1995 to May 2015

- Science Citation Index Expanded (Web of Science) 1899 to May 2015
- Conference Proceedings Index-Science (Web of Science) 1990 to May 2015
- WHO International Clinical Trials Registry Platform (ICTRP) 2007 to May 2015
- Current Controlled Trials (CCT) 2000 to May 2015
- NIH ClinicalTrials.gov 2000 to May 2015
- Manufacturer and User Facility Device (MAUDE) 1991 to May 2015
- MEDION database

Sensitive keyword strategies using free text and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (e.g., sepsis) were combined with terms for the test (e.g., SeptiFast, SepsiTest and IRIDICA). No language restrictions were used on any database; however, the clinical effectiveness searches were date-restricted. To date, all included rapid molecular tests (SeptiFast, SepsiTest and IRIDICA assay) have received a CE mark for use on whole blood samples. The search strategy of the current review updated the search strategy of an existing review on SeptiFast and amended it within the scope of the current review (i.e., the search strategy was amended to include generic, trademark or other product names of all the relevant index tests, other bacterial or fungal gene terms were added and were combined with polymerase chain reaction [PCR] and population terms and a limit to exclude all only animal studies was introduced). An example of the MEDLINE search strategy is provided in Appendix 1 of the Assessment Report.

Other Resources

To identify additional published, unpublished and ongoing studies, the reference lists of all relevant studies were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. In addition, systematic keyword searches of the World Wide Web (WWW) were undertaken using the Google search engine, key experts in the field were contacted and company submissions were screened for published or unpublished data additional to those identified in studies retrieved from the literature search.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software (version 12.0; Thomson Reuters, Philadelphia, PA).

Inclusion and Exclusion Criteria

The inclusion of potentially relevant articles was undertaken using a three-step process. First all titles were examined for inclusion by one reviewer. Any citations that clearly did not meet the inclusion criteria (e.g., non-human, unrelated to sepsis) were excluded. Second, all abstracts were examined independently by two reviewers and the full manuscript of all potentially eligible articles that were considered relevant was obtained, where possible. Third, two reviewers independently assessed the full-text articles (n=177) for inclusion. All potential included studies (n=87) were then adjudicated by three clinical experts independently. Any disagreements in the selection process were resolved through discussion and included by consensus between the two reviewers and three clinicians. The relevance of each article for the systematic review was assessed according to the following criteria:

Study Design

All clinical diagnostic accuracy studies that evaluated the index test with standard culture results (with or without matrix-absorbed laser desorption/ionization - time of flight mass spectrometry [MALDI-TOF MS]) on patients' whole blood samples during the management of suspected sepsis were included. In reviews of test accuracy the 'index test' (the test whose performance is being evaluated) can be viewed as the intervention.

Reviews of primary studies were not included in the analysis but were retained for discussion and identification of additional studies. Moreover, the following publication types were excluded from the review: animal models; biological studies; narrative reviews, editorials and opinions; case reports; non-English-language papers and reports published as meeting abstracts only when insufficient methodological details are reported to allow critical appraisal of study quality.

Population

All studies of adults and children (of any age) with suspected blood stream infections in secondary care (i.e., departments and wards providing care for acutely unwell patients and/or critical care units) who required blood cultures were included. Potential subgroups of interest included: people with a suspected health care associated infection, people with a suspected community acquired infection, children and neonates, people who are immunocompromised and people exposed to antibiotics prior to blood sample collection. Following clinical advice, people with febrile neutropenia were also considered as potential subgroup of interest. This group of patients usually undergo blood culture testing as their ability to

show the classical signs of sepsis are impaired and failing to treat an underlying infection can result in mortality. This practice is supported by a recent large retrospective study which found that a significant number of poor outcomes from severe systemic infection occur in the absence of systemic inflammatory response syndrome (SIRS) criteria at inception.

Target Conditions

Suspected sepsis, including severe sepsis and septic shock as defined by Levy et al. (2003).

Interventions (Index Test)

The following tests (in conjunction with clinical assessment) performed on whole blood samples for the detection of bloodstream bacterial and fungal pathogens were included:

- SeptiFast
- SepsiTest
- IRIDICA assay (extended to include preceding versions of the test if the authors believed that the data were likely to be generalisable to IRIDICA assay)

Comparator Test (Reference Standard)

The reference tests included current standard care to define the target condition, which included blood culture (in conjunction with clinical assessment) for the identification of bloodstream bacterial and fungal pathogens with or without MALDI-TOF MS. Where studies were identified that included more than one intervention then these would also form comparators for each intervention.

Outcomes

Refer to the "Major Outcomes Considered" field.

Clinical Effectiveness Results

Number of Studies Identified/Included

The literature searches identified 2892 citations. Of these, 66 studies met the inclusion criteria. A flow chart describing the process of identifying relevant literature can be found in Figure 2 of the Assessment Report.

Assessment of Cost-effectiveness

Systematic Review of Existing Economic Evidence

Methods

A systematic search of the existing published literature evaluating the economic impact of the SeptiFast, SepsiTest and IRIDICA tests to rapidly detect and identify bacterial and fungal deoxyribonucleic acid (DNA) which may be present in the bloodstream in people who are suspected of having sepsis was undertaken.

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (OvidSP) 1948 to May 2015
- EMBASE (OvidSP) 1980 to May 2015
- Cochrane Database of Systematic Reviews (Wiley Online) 1996 to May 2015
- Cochrane Central Register of Controlled Trials (Wiley Online) 1898 to May 2015
- Health Technology Assessment Database (Wiley Online) 1995 to May 2015
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- Conference Proceedings Index-Science (Web of Science) 1990 to May 2015
- WHO International Clinical Trials Registry Platform (ICTRP) 2007 to May 2015
- Current Controlled Trials (CCT) 2000 to May 2015
- NIH ClinicalTrials.gov 2000 to May 2015
- Manufacturer and User Facility Device (MAUDE) 1991 to May 2015
- MEDION database

Sensitive keyword strategies using free text and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (e.g., sepsis) and the test (e.g., SeptiFast, SepsiTest and IRIDICA) were combined with a search filter aimed at restricting results to economic and cost-related studies (used in the searches of MEDLINE and EMBASE). No language restrictions were used on any database; however, the searches were restricted by date. In brief, CE approval for the oldest rapid molecular test (i.e., SeptiFast) was obtained in 2006. As a result, no relevant economic evaluations were expected to be published prior to this date. An example of the MEDLINE search strategy is provided in Appendix 6 of the Assessment Report).

Other Resources

To identify additional published, unpublished and ongoing studies, the reference lists of all relevant studies were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. In addition, systematic keyword searches of the WWW were undertaken using the Google search engine, key experts in the field were contacted and company submissions were screened for published or unpublished data additional to those identified in studies retrieved from the literature search.

Studies were selected for inclusion according to pre-determined inclusion and exclusion criteria. A summary of these criteria are provided in the table below.

Studies were selected for inclusion through a two-stage process:

- Level 1 screening: Titles and abstracts were independently examined for inclusion by two reviewers. Any disagreements in the selection process were resolved through discussion.
- Level 2 screening: Full manuscripts of selected citations were then retrieved and assessed by one reviewer. A second reviewer performed an independent quality check to ensure that the inclusion criteria were applied correctly. Any disagreements in the selection process were resolved through discussion.

Table: Inclusion and Exclusion Criteria for the Review of Economic Evaluation

Criteria	Included	Excluded
Countries	All	No restrictions
Settings	All	No restrictions
Study design	Economic evaluations (model or study-based) comparing one of the intervention listed below versus an appropriate comparator, including other interventions if applicable	• Non-economic evaluation • Cost study of one test only (comparison of costs of different reagents or techniques)
Population	Adults and children (of any age) with suspected blood stream infections in secondary care (i.e., departments and wards providing care for acutely unwell patients and/or critical care units) who required blood cultures were included	
Target condition	People with suspected sepsis	People who do not have suspected sepsis
Comparator test	Blood culture with or without matrix-absorbed laser desorption/ionization - time of flight mass spectrometry (MALDI-TOF MS)	Other tests done in house
Interventions (index test)	• SeptiFast • SepsiTest • IRIDICA	Economic evaluations that do not investigate one of the interventions of interest in at least one of the arms
Outcomes	• Cost-minimisation • Cost-effectiveness • Cost-utility analysis	

Results

A total of 89 citations were retrieved. Of these 77 citations were identified via database searching and an additional 12 citations were retrieved through other sources. (See Figure 10 of the Assessment Report for the flow chart for economic review.)

Four studies (corresponding to four references) were identified as meeting the inclusion criteria of the systematic review of economic evaluations.

Five papers were excluded after retrieval of the full papers. The rationale being: results published in full elsewhere; other interventions; absence of economic evaluation and inappropriate intervention.

Number of Source Documents

Assessment of Clinical Effectiveness

Sixty-six studies were included in the review.

- Sixty-two of the 66 studies were included in meta-analysis.
- Forty-one of the 66 studies were included in narrative synthesis.

Refer to Figure 2 in the Diagnostics Assessment Report (DAR) (see the "Availability of Companion Documents" field) for a study flow chart.

Assessment of Cost-effectiveness

- Four studies (3 full text studies and 1 poster) were included.
- An economic model was presented by the External Assessment Group.

Refer to Figure 10 in the DAR for a study flow chart.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Data Abstraction Strategy

Data abstraction was performed by one of three reviewers into a standardised data extraction form and independently checked for accuracy by a second reviewer. Discrepancies were resolved by discussion between the two reviewers and if agreement could not be reached, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Moreover, as this review of three rapid molecular tests incorporated an update of the most recent review of SeptiFast, all relevant data was extracted from the systematic review in the first instance, but were cross checked for accuracy with the original papers. When necessary, additional data was

extracted from the original papers. For the review of SepsiTest and IRIDICA, all data was extracted from the original papers. Unpublished study data from the company (which was received during the review process) that met the inclusion criteria, were also extracted and quality assessed in accordance with the procedures outlined in the Assessment Report.

The following information was extracted for all studies when reported: study characteristics (e.g., author, year of publication, country, study design, setting, funding); participant details (e.g., age, sex, inclusion and exclusion criteria); test details; reference standard details; and outcomes (including definitions).

Quality Assessment Strategy

The methodological quality of each included study was assessed by one of three reviewers and independently checked by a second reviewer. Disagreements were resolved by discussion between the two reviewers and if agreement could not be reached, a third reviewer was consulted. The study quality characteristics were assessed according to (adapted) criteria based on those proposed by Whiting et al., (Quality Assessment of Diagnostic Accuracy Studies [QUADAS]-2) Further details are provided in Appendix 2 of the Assessment Report.

Methods of Data Synthesis

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description. The analysis comprised a narrative synthesis and pair-wise meta-analysis.

Meta-analysis

Where sufficient data existed, a meta-analysis was undertaken to generate pooled estimates of diagnostic parameters. The number of true positives, false negatives, false positives and true negatives from each study was meta-analysed to estimate sensitivity and specificity under the assumption that blood culture was 100% sensitive and specific. In brief, a bivariate normal model was used to model the population logit sensitivities and population logit specificities in each study to account for correlation between sensitivity and specificity within studies.

All parameters were estimated using Markov Chain Monte Carlo simulation implemented using the WinBUGS software package. Analyses were conducted in R using the R2WinBUGS interface package. Convergence was assessed using the Gelman-Rubin convergence statistic. Convergence was achieved relatively quickly and generally within 5,000 iterations; in practice, a burn-in of 10,000 iterations was used. There was no evidence of high autocorrelation between successive samples of the Markov chains. Results were displayed as forest plots and summary receiver operating curve (SROC) plots with 95% credible intervals (CrIs) and 95% prediction intervals (PrIs) for sensitivity and specificity.

Narrative Synthesis

A meta-analysis was not conducted on a range of intermediate measures and clinical outcome measures as the necessary data were not available or it was inappropriate to statistically pool studies because of their variability in reporting outcome data. Therefore, as suggested by the guidance produced by the Cochrane Collaboration and the Centre for Reviews and Dissemination (CRD) for undertaking systematic reviews, a narrative synthesis of included studies (grouped by outcome) was undertaken.

See Section 2 of the Assessment Report for additional information on clinical effectiveness analysis.

Assessment of Cost-effectiveness

No formal quality assessment of the existing cost-effectiveness evidence was conducted. When assessing the methodological quality of the economic literature, a number of checklists are available; however, quality assessment checklists for assessing economic evaluations of diagnostic tests are limited. Similarly, the majority of checklists focus on the quality of reporting rather than the methodological quality of a study. Due to these limitations the relevance of each study to the decision problem is discussed within Sections 3.1.2.2, 3.1.2.3 and 3.2 in the DAR.

Independent Economic Assessment – Conceptual Model and Methods

The conceptual model developed by the External Assessment Group was relatively simplistic due to the lack of appropriate data. A decision tree approach was adopted with a lifetime horizon and discounting undertaken at 3.5% per annum.

Within the model it was assumed that the rapid identification of a pathogen could result in changes in four key outcomes. These were: 30-day mortality rates; the length of stay in an intensive care unit (ICU); the length of stay in the hospital; and the costs associated with antimicrobial treatment. Of these, changes in the mortality rate were assumed to affect quality-adjusted life years (QALYs) only, with the remaining categories assumed to affect costs only. This is a simplification in that, for example, additional time in an ICU may be associated with slightly lower QALYs, but the impact of such omissions was assumed not to affect the overall conclusions. In all scenarios the potential impact of better antimicrobial stewardship in terms of drug resistance was not evaluated due to both the complexity of such a task and the absence of information on how the

tests would reduce antimicrobial use.

It was assumed that negative tests would not impact on any of the four key outcomes. This assumption was supported by the clinical experts to the External Assessment Group. The decision to ignore negative tests was due to the potential fatal consequences if treatment was withdrawn from a patient with sepsis. Acknowledged reasons for a false negative result include the pathogen being unable to be detected by the test or if the quantity of the pathogen was below the test's limit of detection. Similarly tests which would be denoted as failures were assumed to have no impact on the four key outcomes. Both negative tests and failures would, however, be associated with the cost of the test.

A pictorial representation of the conceptual model is provided in Figure 11 of the Assessment Report. The net cost impact and the net QALY impact of rapid identification were used to estimate a cost per QALY gained ratio.

See Section 3 of the Assessment Report for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostics Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs; the degree of clinical need of patients under consideration; any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State; and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Economic Analysis Results

Five deterministic analyses were done:

- Base case 1: interventions compared with blood culture, with clinical-outcome data taken from the systematic review
- Base case 2: interventions compared with blood culture, with clinical-outcome estimates taken from expert opinion
- Threshold analyses
- Interventions compared with matrix-absorbed laser desorption/ionization - time of flight mass spectrometry (MALDI-TOF MS)
- Data taken from studies comparing more than 1 intervention

Base Case 1 Results

The results of the analysis showed that all the interventions were dominated by blood culture (that is, blood culture was less expensive and more effective than all of the interventions). Regardless of the test throughput assumed in different scenarios, the interventions remained dominated (more expensive with no additional clinical benefit) because of the lack of quality-adjusted life years (QALYs) gained.

In addition, a threshold analysis was done for base case 1 to assess the reduction in antimicrobial costs that would be needed for each intervention to be cost neutral. The results suggested that the reductions needed would be 44% to 59% for the LightCycler SeptiFast Test MGRADE, 31% to 43% for the SepsiTest and 56% to 90% for the IRIDICA BAC BSI, although the rate of positive tests associated with each intervention suggested that their costs could not be offset solely by a reduction in antimicrobial therapy use.

Base Case 2 Results

In all scenarios modelled for this test, MALDI-TOF MS produced a positive net benefit compared with blood culture. In 1 scenario (30-day mortality rate 13%, 2.4 tests per day, maximum acceptable incremental cost-effectiveness ratio [ICER] of £20,000 per QALY gained), SepsiTest had the highest net monetary benefit when it was assumed that equipment to run the test had to be bought. In the same scenario, the IRIDICA BAC BSI assay had the highest net monetary benefit when only the test reagents and consumables were purchased. In all other modelled scenarios, the IRIDICA BAC BSI assay had the highest net monetary benefit.

Threshold Analyses

The External Assessment Group used a range of threshold analyses to explore the effect of key clinical outcomes. In all analyses, it was assumed that the comparator equipment had already been bought but that the equipment for the interventions needed to be bought. The threshold levels resulting from the analyses, which assumed 2.4 tests run per day and a maximum acceptable ICER of £20,000 per QALY gained, suggested reductions in 30-day mortalities ranging from 0.09 to 0.14 per 100 tests would be needed for the interventions to be considered cost effective compared with blood culture. Antimicrobial costs would need to reduce by £149.53 to £314.61 per 100 tests. The results were similar when the interventions were compared with MALDI-TOF MS. The threshold analyses that assumed either 17 or 68 tests run per day produced lower threshold values. The values of the reductions needed were also lower when a maximum acceptable ICER of £30,000 per QALY gained was assumed.

Cost-effectiveness of the LightCycler SeptiFast Test MGRADE and SepsiTest Compared with MALDI-TOF MS

The External Assessment Group also explored the cost-effectiveness of both the LightCycler SeptiFast Test MGRADE and SepsiTest compared with MALDI-TOF MS, based on data from 2 studies that used MALDI-TOF MS in addition to blood culture. The effect estimates based on expert opinion were also included in the analysis. It was assumed that both interventions had a failure rate of 0% and that equipment to run the tests needed to be bought. The results of these analyses suggested that when compared with MALDI-TOF MS (and blood culture), the LightCycler SeptiFast Test MGRADE dominated (less costly and more effective) MALDI-TOF MS (and blood culture), and SepsiTest had ICERs ranging from £23,375 to £34,848 per QALY gained with a 30-day mortality rate of 13% and from £10,479 to £15,621 per QALY gained with a 30-day mortality rate of 29%.

Results from Studies Comparing the LightCycler SeptiFast Test MGRADE and SepsiTest Simultaneously with Blood Culture

An analysis was run using data from 2 studies, which evaluated both the LightCycler SeptiFast Test MGRADE and SepsiTest with blood culture.

The analysis was done to compare the relative cost-effectiveness estimates with those derived in base case 2 that were based on indirect comparisons of the relative effectiveness of the interventions from expert opinion. The analysis assumed a 0% test-failure rate for both interventions and that equipment to run the tests needed to be bought. A range of scenarios were presented with 30-day mortality rates of 13% or 29% and a throughput of 2.4, 17 or 68 tests per day. In all scenarios, the ICER for the LightCycler SeptiFast Test MGRADE was greater than £30,000 per QALY gained when compared with SepsiTest.

Refer to Sections 4 and 5 of the original guideline document for additional information on cost-effectiveness.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group (EAG), to the Committee and later publishes these comments on its Web site.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The Diagnostics Advisory Committee (DAC) considered a systematic review and an economic model prepared by an External Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The rapid detection and identification of bacterial and fungal deoxyribonucleic acid (DNA) may be particularly beneficial in people who are suspected of having a severe infection and who need quick medical intervention.

Potential Harms

The tests may result in false positives and false negatives. For false positives there is the risk of over-treatment which would incur cost and could increase the risk of antimicrobial resistance; for false negatives, if treatment was withdrawn the patient could be at increased risk of morbidity and mortality.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate

to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay). London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 10. 46 p. (Diagnostics guidance; no. 20).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Feb 10

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Stevenson M, Pandor A, Martyn-St James M, Rafia R, Uttley L, Stevens J, Sanderson J, Wong R, Perkins G, McMullen R, and Dark P. Sepsis: the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. A systematic review and economic evaluation. Diagnostics assessment report. Sheffield (UK): School of Health and Related Research Technology Assessment Group (ScHARR-TAG), University of Sheffield; 2015 Jul. 380 p. Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay). Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. (Diagnostics guidance; no. 20). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

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